

COVID-19 World Tour: Glucose fan-support

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Abstract

In this unprecedented period of quarantine, countless questions are purported about COVID-19. While the scientific community searches for answers, the rest of the world is desperately waiting for evidence-based methods of prevention. Yet, one method has been known in virology for decades; viral replication depends on a glucose environment in the host. In fact, pre-existing metabolic dysregulation cripples the immune system and increases susceptibility to pathogens. According to figures by the US Department of Health (30 March, 2020), diabetes, pre-diabetes, kidney disease and obesity mark the most dangerous comorbidities in COVID-19 deaths. Patients with chronic metabolic comorbidities including strokes, CHD/CVD, unregulated diabetes and hypertension comprise 95% of New York and 99% of Italy's COVID-19 deaths [1]. Older adults and those with serious underlying medical conditions are at the highest risk for developing the most severe complications from the Coronavirus [1]. Complications arising from comorbidities often have their deepest roots in poor nutrition. Reversing metabolic pathology to increase systemic immunity via reversal of glucose dependency and restoration of metabolic inflexibility has been well established in the literature. The lethal impact of COVID-19 and of future viral pathogens could be greatly diminished by stabilization of metabolic fuel flux through nutritional modifications, which are easily measured and tracked via reductions in the following inexpensive blood tests: HgA1c, HOMA-IR (Homeostatic model assessment of Insulin Resistance-fasting blood glucose/fasting insulin), triglycerides and the triglyceride/HDL ratio. Establishing self-efficacy through patient-centered biological education with implementation of bio-individualized lifestyle coaching holds great promise to slow the worldwide trajectory of underlying metabolic conditions associated with poor COVID-19 prognosis. This review examines the physiological mechanisms of metabolic flexibility, the importance of the nutritional status of the host in viral infection and the influence of glucose dependency on viral replication, namely COVID-19.

Keywords: COVID-19 • Metabolic Syndrome • Diabetes • Obesity • mTor • AMPK • Glycolysis • Metabolic Flexibility • Immunity • Ketogenic diet • Vitamin/Mineral supplementation

Introduction

Most agree that a diet of nutritious whole foods promotes a healthy immune system. Consuming a variety of nutrient-dense, antioxidant rich foods, while maintaining a homeostatic balance of essential vitamins/minerals like zinc, selenium, Vitamin E, and Vitamin C contributes to robust immune function [2]. However, globally prevalent poor dietary habits significantly increase risk factors for weakened immunity [3]; therefore, it is imperative in every context to explore ways to modify nutritional status to strengthen internal defenses. Viral replication is highly dependent upon glucose dependency caused by poor dietary practices. Additionally, deficits in zinc, selenium, Vitamin D and Vitamin C are signposts of the ever-growing phenomenon of diabetes; a Westernized phenotype marked by overfeeding juxtaposed with malnourishment [3].

The Immune System

The action of the immune system includes both the innate and adaptive responses. The innate response is the first responder to an invading pathogen. Cells respond by producing phagocytes (e.g., macrophages and monocytes), neutrophils, dendritic cells, mast cells, eosinophils, and other white blood cells of defense. Vitamin D, Vitamin E, and zinc have been found to be integral to a healthy, innate immune response. Vitamin D stimulates the replication of monocytes and macrophages, while Vitamin E and zinc protect against oxidative damage and excessive inflammation [4]. The adaptive

immune response involves action from cytotoxic T cells, T helper cells, and B cells. Cytotoxic T cells work to destroy infected cells, while the T helper cells coordinate responses of other immune cells. The B cells are in charge of the production of immunoglobulins, also referred to as antibodies. Immunoglobulins have the ability to bind to specific viruses to slow them down and help them be destroyed by the rest of our immune system. Once the pathogen has been recognized, T and B cells are able to form "memory cells", which can mass produce the effective cellular defenders for a specific antigen. Again, these powerful immunomodulators on the front line of viral attack are dependent on the availability of essential vitamins and minerals as cofactors. A robust immune system depends on a healthy diet. Selenium, a dietary antioxidant found in nuts, seeds, eggs and fish works in a functional, structural, and enzymatic role, in a range of proteins involved in optimal immune function. Likewise, vitamin A and D are transcriptional factors that regulate cell division essential to successful and controlled proliferative responses in the immune system [2]. Notably, the gastrointestinal tract (GIT) contains roughly 80% of the body's immune cells directly beneath its thin epithelial layer; fine tuning of immunity is orchestrated by the neurons of the enteric plexuses, buried deep in the layers of mucous and smooth muscle of the GIT. Afferent neurons synapsing from the plexuses relay communication to the CNS about the host's nutritional status received from the enterochromaffin incretin cells lining the small intestine. Nutritional status gets relayed to the CNS for modification of immunity via vagal tone. Nutrition is a powerful immune modulator.

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Received: 09 June, 2020; **Accepted:** 11 June, 2020; **Published:** 22 June, 2020

Viruses: How do they work?

Most viruses, including COVID-19, are airborne and require a mode of droplet transportation to spread among people. Sneezing, coughing or transmission of other bodily fluids is the primary method. The virus makes contact with human tissue and begins the process of parasitic invasion. In general, viruses have particular targets based on unique surface proteins. For example, COVID-19 targets the ACE2 receptors on the lungs, which leads to serious respiratory problems via invasion of the alveoli that culminates in dysregulated inflammation known as ARDS (acute respiratory distress syndrome). The primary goal of a virus is parasitic hijack of the machinery within healthy cells; without a viable host, a virus is lifeless and powerless due to its inability to proliferate. Instead, viruses attach to unhealthy cell membranes and penetrate the nucleus to hijack the host's RNA/DNA resulting in the replication of new viruses. This process typically kills the host cell allowing the virus to burgeon. The necrotic cells left in the wake of viral hijacking lead to the activation of a deadly, irreversible inflammatory response. A proper understanding of viral physiology is critical when considering nutrition modes of prevention of COVID-19.

Vitamins and Minerals: Imperative to Immunity

A healthy immune system defends against viruses by denying the initial attachment/infiltration via recognition of compromised/infected cells. Antibodies bind to viruses and physically prevent them from infiltrating, buying time for the entirety of the immune system to destroy the foreign invaders. Furthermore, the immune system is very adept at recognizing cells that are sick or malformed. A healthy immune system can recognize a cell that has been hijacked by a viral pathogen and destroy it via natural killer cells and cytotoxic T cells before damage has occurred in the body [5]. While the immune system is a powerful and efficient machinery, at times it becomes overactivated or weakened failing to respond effectively to pathogen invasion. A pervasive, world-wide risk factor for dysregulated immunity is malnutrition [3]. There are several fundamental vitamins and minerals that are crucial to immune function including zinc, selenium, Vitamin C and Vitamin E. Vitamin and mineral deficiencies diminish immunity, thereby increasing the risk for contracting COVID-19 as well as other opportunistic pathogens.

Selenium and Vitamin C are powerful antioxidants in the body that remove free radicals and promote an anti-inflammatory tissue response. The leukocytes of the immune system can suffer oxidative damage over time if exposed to free radicals too often; antioxidants work to keep the immune system healthy by neutralizing harmful oxygen species [6]. Zinc is also crucial to cellular immunity. It is an important cofactor in the development of natural killer cells and neutrophils that help to activate genes in the immune response, while decreasing oxidative stress and inflammatory cytokines [7]. While several vitamins and minerals are helpful in boosting immunity, selenium, Vitamin C, Vitamin E and zinc are cornerstones of a robust immune response.

Excess Glucose: The Silent Killer

Proper nutrition has a profound impact on the immune system in regard to homeostatic blood glucose levels. Scientific literature generally agrees that viruses thrive in glucose-fed environments; the virus becomes more virulent and dangerous inside a host with elevated blood glucose [8]. A study examining viral influenza found that viral infections thrived under abundant glucose supply [9]. The human body relies on three primary macronutrients; two of those are used for immediate energy: carbohydrates (glucose) and lipids (fatty acids). The physiological Randle Cycle explains the cellular "order of burn" for these fuels. The body will utilize macronutrients in a

specified evolutionary order: glucose, fatty acids, protein. While carbohydrates are the primary default fuel due to the evolutionary importance of glucose oxidation especially for the brain, the overconsumption of carbohydrate rich foods, and ensuing insulin resistance, inhibits metabolic flux between fat and glucose. This causes chronic hypoglycemia and a repetitive, cortisol driven stress response with impaired immune function [9].

Healthy physiology cycles through two physiological states that determine enzyme action, immunity, growth and repair: the Fed and Fasted states. In the Fed state, the body is programmed through activation of the mTOR protein energy sensing pathway to redistribute incoming energy via biosynthesis, growth and storage. The body accumulates energy reserves and stimulates endergonic actions. While this Fed state metabolism is healthy and essential in the short term under cyclical flexibility, chronic activation of the endergonic, Fed cycle increases the likelihood of cellular damage, excessive proliferation and pathogen invasion.

In contrast, the fasted state commences when glucose and insulin clear from the bloodstream. The low- insulin state triggers the AMPK nutrient sensing pathway for recycling, repair, cellular clean-up, and marks a shift to fatty acid oxidation as the primary metabolic fuel. Metabolic flexibility is a hallmark of longevity/immunity and refers to the cells' ability to transition smoothly between glucose and fat as fuel sources without hypoglycemic episodes. However, when cells are chronically stuck in a Fed state, the body becomes glucose dependent relying solely on aerobic/anaerobic glycolysis devoid of beta-oxidation. The constant influx of glucose promotes adiposity, increased risk of cancer and elevated susceptibility to pathogenic viruses like COVID-19 [9].

A landmark study by Kohio and Adamson [9] found, "higher glucose levels led to an increase in viral protein accumulation within infected cells" (p. 307). Kohio and Adamson observed a significant increase in the percentage of infected cells as the plasma glucose levels climbed (72-108 mg/dL), compared to the control group (60 mg/dL) ($P \leq 0.05$). To test the effects of glucose's utilization in the cells, researchers conducted an experiment involving the inhibition of aerobic glycolysis. Glycolysis is the mechanism by which cells break down glucose into energy. By inhibiting enzymes necessary to this pathway, the researchers found that "viral infections were reduced by at least 90% with 2-DG treatment and by at least 80% with 3-BrPa treatment when compared to the control treatments" (p. 308) [9]. By inhibiting a key enzyme in the glycolytic pathway, hexokinase, cells were unable to access the energy in glucose. By circumventing the glucose default pathway for energy, both cancer and viral infections decreased significantly [9]. A healthy diet that regulates the fed/fasted cycles and purports to mediate the natural tendency toward glucose dependency has the potential to significantly reduce the risks associated with COVID-19 pandemic.

Metabolic Syndrome Alters Immunity

Individuals at the highest risk for COVID-19 infection and complications are those with comorbidities including hypertension, diabetes and obesity; these are the same individuals who are metabolically inflexible. Modulating the fed/fasted cycles via nutrition reduces the states of comorbidity and increases the likelihood of immunity against COVID-19 by enhancing immune functionality. As explained by Osbron and Olefsky [10], "Obesity is the most common cause of insulin resistance, and the current obesity epidemic in the United States and other Western countries is driving a parallel type 2 diabetes epidemic" (p. 372) [10]. Diabetes and obesity have been shown to dramatically down-regulate the immune system and increase oxidative damage and stress. Reversing metabolic syndrome at the core of the disease by starting with modifications in diet to restore metabolic flexibility, will dramatically improve the body's ability to defend itself from the parasitic invasion of COVID-19 [9].

Conclusion

Patients diagnosed with diabetes and obesity typically have several comorbidities; however, a staggering number of people remain undiagnosed. Metabolic pathologies perpetuated by a poor diet will lead to systemic disease and increased risk for parasitic invasion. Diet affects the entire body via modification/manipulation of master nutrient sensing pathways that regulate overall homeostasis. It is imperative to understand the power of proper nutrition, especially in the midst of a world-wide pandemic. The Coronavirus is a viral infection that must be taken seriously, but central to the proactive prevention of the disease must be a discussion/education on healthy nutrition, vitamin/mineral supplementation and the maintenance of metabolic flexibility. Malnutrition leads to suppressed immunity and systemic disease; this includes the overfed-undernourished phenotype [11]. By controlling blood glucose levels and allowing the body to exit the glucose-driven mTOR path and transition to the exergonic, AMPK fat-oxidizing path, the body gains vital weaponry against invading pathogens that depend on glucose environments. No one knows the future of COVID-19; the only surety is this will not be the last pathogen to make a World Tour.

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How to cite this article: Wyk Jake Van, Nick Banfield and Kelly Gibas. "COVID-19 World Tour: Glucose fan-support ". *J Metabolic Syndr* 9 (2020) doi: 10.37421/JMS.2020.9.254